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## **Microglia: a novel treatment target in gliomas**

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## Microglia: a novel treatment target in gliomas

Microglial cells have not received too much attention in Neuro-Oncology over the last decades, despite the fact that they may be the most abundant cell within the glioma tissue. Accordingly, *Neuro-Oncology* now devoted a major review article on the changing concepts of what microglial cells do or do not do, both in the normal and diseased brain, with a focus on the biology of gliomas (1).

Traditionally, microglial cells have been considered part of the immune system, but it had remained controversial to what extent these cells are capable of antigen presentation and participation in immune responses. Their origin, local resident brain cell *versus* bone marrow-derived, has been one focus of microglia research for years, and it now seems clear that the microglial cell population especially in the disease state is likely to derive from both cellular sources.

The current view sees microglial cells not as an efficient arm of the immune system, but rather a misguided host cell population abused by the growing glioma for its own advantage. Microglial cells are attracted to the site of tumor growth and expanded locally by signaling molecules such as monocyte chemoattractant protein 1, macrophage colony-stimulating factor, vascular endothelial growth factor and placental growth factor. These factors are not only released by glioma cells, but presumably also by the microenvironment that is constantly shaped by these tumors. Thus, microglial cells are now thought to support invasiveness by the release of matrix metalloproteases, angiogenesis by the release of proangiogenic factors, and immunosuppression. The latter is mediated by the conversion of microglial cells, respectively macrophages recruited from the periphery, into the M2 macrophage

phenotype which is characterized by the release of immunosuppressive, e.g. interleukin 10, rather than immunostimulatory cytokines, e.g. tumor necrosis factor- $\alpha$  or interferon- $\gamma$ , less nitric oxide production, and poor antigen presentation. These changes in the microglia/macrophage phenotype, in turn, are thought to be controlled by soluble factors such as transforming growth factor- $\beta$  which interact with their respective receptors expressed on microglial cells.

Altogether, these considerations may lead to new treatment approaches for glioblastoma that focus not only on the glioma cells proper, but raise the perspective of trying to contain glioma growth by modulating its microenvironment, notably its permissiveness for immune responses against the tumor. Thus, any immunotherapy will work better if the M2 phenotype of microglial cells and macrophages can be (re)converted to a M1 phenotype.

Finally, if microglial cells are indeed in part bone marrow-derived and exhibit efficient homing into the brain, cellular therapy strategies might adopt some of the pathways mediating this specific cellular trafficking between periphery and central nervous system to deliver therapeutic payloads to the intracranial tumor sites or even directly use engineered, reprogrammed microglial cells for such purposes.

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1 Li W, Gräber M. The molecular profile of microglia under the influence of glioma.

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